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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/823,999
Filing Date: March 25, 1997
Appellant(s): ROGERS ET AL.

Patrea Pabst
For Appellant

SUPPLEMENTAL EXAMINER'S ANSWER

This is in response to the **Reply Brief** filed 3/5/05.

Given newly presented arguments addressing evidence of record or mischaracterizing the evidence and positions of record in conjunction with newly presented arguments set forth in the **Reply Brief**, this **Supplemental Examiner's Answer** is set forth herein.

This **Supplemental Examiner's Answer** follows the numbering and labeling of issues according to the **Reply Brief** for clarity.

A more complete analyses of the Issues under appeal is set forth in the **Examiner's Answer**, mailed 12/9/04.

3) STATUS OF CLAIMS.

In response to appellant's statement in the **Reply Brief** concerning the status of the Claims, the following is reiterated from the **Examiner's Answer**, mailed 12/9/04.

The statement of the status of claims contained in the **Substitute Appeal Brief** is correct.

Claims 1-12 are pending.

Claims 7 and 9 have been withdrawn as directed to a non-election invention for the purposes of this appeal.

Claims 1-6, 8 and 10-12 are under consideration as the claims read on ant-Mac-1 (anti-CD11b/CD18) antibodies as the claimed "compound, which specifically inhibits or reduces leukocyte integrin-mediated adhesion of function in patients undergoing certain cardiovascular surgeries or procedures".

For clarity and in the interest of compact prosecution, the purpose of previously indicating that non-elected claims 7 and 9 were subject to the rejections under 35 USC § 112, first paragraph, written description and enablement during prosecution was to put appellant on notice that these claims would be similarly rejected under 35 USC § 112, first paragraph.

Although appellant asserts that the examiner has adopted a completely inflexible approach, appellant has not set forth exactly what is the nature of the completely inflexible approach and how it does not comport with the law.

In contrast to appellant's assertions of an inflexible approach by the examiner, the examiner maintains that the rejections of record have been in concert with appropriate legal standards.

(6) ISSUES ON APPEAL

With respect to appellant's statements concerning the Issues on Appeal, the following is reiterated from the **Examiner's Answer**, mailed 12/9/04.

Appellant's statement of the issues in the **Substitute Appeal Brief** is correct with the exception of the following.

Issues 1 and 2: For clarity and in the interest of compact prosecution, the purpose of previously indicating that non-elected claims 7 and 9 were subject to the rejections under 35 USC 112, first paragraph, written description and enablement during prosecution was to put appellant on notice that these claims would be similarly subject to these rejections under 35 USC 112, first paragraph, in the interest of compact prosecution.

Claims 7 and 9 have been withdrawn from consideration in the instant application.

Upon reconsideration, and in view of appellant's amended claims, the previous rejection under 35 USC §112, first paragraph, enablement with respect to claim 10 has been withdrawn.

Issue 3: The previous rejections under 35 USC § 112, second paragraph, have been withdrawn in view of applicant's amended claims and upon reconsideration of metes and bounds of "stenosis" and "restenosis". See **The Invention and Clarification of Terms** in the **Response to Argument** in the Examiner's Answer).

Upon the abandonment of USSN 09/776,533, the previous provisional rejection under the grounds of obvious double patenting has been withdrawn.

REPLY TO EXAMINER'S ANSWER

(a) Rejections Under 35 U.S.C. § 112, First Paragraph

(i) Written Description

Claims 1-6, 8 and 11-12 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a **written description** of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

As pointed out previously and reiterated above in **(3) STATUS OF CLAIMS,**
claims 1-6, 8 and 11-12 stand rejected under 35 U.S.C. § 112, first paragraph, and not claims 1-9 and 11-12 as indicated by appellant on page 5 of the **Reply Brief**.

However, the examiners agrees with appellant to the extent that the rejections under 35 U.S.C. § 112, first paragraph, written description (and enablement set forth in (ii) below) would be applicable to non-elected / withdrawn claims 7 and 9, as these withdrawn claims recite targets of the claimed compounds, wherein appellant has not satisfy the statute with respect to the claimed "compounds themselves, wherein said compounds encompass **un**described molecules, peptides and peptidomimetics, which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function", broadly encompassed by the claimed methods.

While appellant asserts that they have relied upon the disclosure and use of known compounds for a new use, the claimed compounds are drawn to "molecules which inhibit expression of the integrins or integrin-ligands and peptides and peptidomimetics derived from the integrins or integrin-ligands which block the interaction of the integrins or integrin-ligands with vascular cells or tissues".

See **claim 1**.

While appellant draws attention to certain known integrins and antibodies to said integrins on pages 8-10 of the instant **specification**, the claimed compounds are broader than the known integrins and antibodies to said integrins.

Appellant also submits that the claims on appeal encompass a genus of compounds complementary to a targeted molecule and inhibits the function of the targeted molecule (see page 7, paragraph 1 of the **Reply Brief**).

In contrast to appellant's reliance on the standard that "mere idea or function is insufficient for written description; isolation and characterization at a minimum are required" (see page 8 of the **Examiner's Answer**) adapted from Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (CAFC 1991). ("Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required.");

the examiner does agree with that position that the legal standard is met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

See Enzo Biochem., Inc. v. Gen-Probe Incorporated 69 USPQ2d 1609 (Fed. Cir. 2002).

Appellant has been directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Also, see MPEP 2163.

Further, the Court has interpreted 35 U.S.C. §112, first paragraph, to require the patent specification to "describe the claimed invention so that one skilled in the art can recognize what is claimed. Enzo Biochem, Inc. v. Gen-Probe Inc, 63 USPQ2d 1609 and 1618 (Fed. Cir. 2002). In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's "disclosure must allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described." *Id.* (quoting Regents of Univ. of Cal. v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed Cir. 1997)).

To this date, appellant has not provided sufficient evidence that there is a known or disclosed correlation or the sufficiently detailed relevant identifying characteristics between the structure of the target (i.e. an integrin such as Mac-1 which is the target of the elected anti-Mac-1 antibodies) and the structure of the claimed compound and its biological activity to inhibit or reduce stenosis or restenosis (e.g. molecules, peptides and peptidomimetics) as it reads on targeting structurally and functionally diverse integrins and their ligands.

While the specification discloses a starting point for screening or testing for compounds that inhibit or reduce leukocyte integrin - ligand interactions, the instant disclosure does not set forth sufficient procedures that will necessarily lead to discovery for such a compound and it does not identify suitable members of compounds such as peptidomimetics, antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds to provide a sufficient number of species to support the claimed genus of "compounds". See paragraph 3 of the Summary of the Invention on page 4 and pages 11-19 of the instant **specification.**

Also, note the absence of any examples of such molecules, peptidomimetics, peptides as compounds disclosed in the specification as-filed, except for the single fibrinogen fragment on page 13, paragraph 3 of the **specification**, wherein said fibrinogen fragment has not been relied upon nor put into evidence to support the claimed methods.

The **specification** discloses only one peptide, that is, a particular fibrinogen fragment which modifies fibrinogen to Mac-1 described by **Altieri et al. J. Biol. Chem. 268: 1847-1853 (1993)** (see page 12, paragraph 3 of the **specification**).

The only observation provided by the specification as filed is the administration of the anti-Mac-1 antibody M1/70 in an experimental animal model (see pages 22-23 of the **specification**).

Again, methods administering "anti-Mac-1 antibodies" read on are the elected invention and considered enabled for the purposes of this appeal.

It is the scope of the general classes of **un**described molecules, peptides and peptidomimetics encompassed by the compounds that are subject to the rejections under 35 USC § 112, first paragraph of record.

In contrast to relying upon the specification as filed or the known compounds at the time the invention was made to support appellant's assertions,

appellant has repeatedly and consistently relied upon either the prior art 7E3 antibody (i.e. ReoPro, abciximab) or post-filing date putative examples of compounds that do not have a nexus to the instant specification, filed 3/25/97, to support the scope of the compounds administered in the claimed methods.

As pointed out previously and in contrast to appellant's assertions of reliance upon known compounds, appellant relies upon

(a) random generation of integrin or integrin encoding sequence binding molecules (e.g. see pages 14-15 of the **specification**);

(b) computer modeling technology (e.g. see page 15, paragraph 1 of the **specification**); and

(c) theoretical calculations and empirical findings for providing guidance for the design of oligonucleotides to inhibit gene expression (e.g. see page 18, lines 25-28 of the **specification**).

In addition, appellant relies upon the statement that "assays for testing compounds for useful activity can be based solely on the interaction of the compound with in the protein (e.g. see page 14, paragraph 1 of the **specification**).

However, no written description of such inhibitory peptides (other than the fibrinogen fragment disclosed on page 13, paragraph 3 of the **specification**), peptidomimetics, molecules or oligonucleotides compounds is disclosed in the specification as filed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

There is insufficient written description of the claimed administered compounds (e.g. molecules, peptides and peptidomimetics) broadly encompassed by the claimed invention. There is a lack of disclosure of sufficient relevant identifying characteristics coupled with a known or disclosed correlation between function and structure of the broadly diverse compounds (e.g. molecules, peptides and peptidomimetics as they read on each structurally and functionally distinct integrin and their ligand) employed in the claimed methods.

The application does no more than describe the desired function of the claimed compounds broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

The claimed methods depend upon finding "a compound that specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis in patients undergoing certain cardiovascular surgery and procedures". Without such a compound, the skilled artisan cannot practice the claimed method of treatment. It means little to invent a method if one does not have possession of the compound(s) that is (are) essential to practice the method. Without possession of the compound(s), the claimed endpoints are illusory and there is no meaningful possession of the method.

Appellant has not provided sufficient identifying or distinguishing characteritistics that support the written description of the genus of the classes of "compounds (e.g. molecules, peptides and peptiodmimeitics) which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" broadly encompassed by the claimed invention.

Therefore as indicated previously, the elected invention of anti-Mac-1 antibodies (and given evidence, certain soluble adhesion molecules and adhesion molecule-specific antibodies as well as the fibrinogen peptide discussed above disclosed in the specification as filed), but not the full breadth of the claimed "compounds", meet the written description provision of 35 USC 112, first paragraph.

It appears that appellant relies upon the targets of claimed compounds
by relying upon the known integrins disclosed on pages 8-10 of the instant specification
as the asserted "known compounds for a new use"
rather that relying upon the written description or possession of "compounds which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" broadly encompassed by the claimed invention,
encompassing molecules, peptides and peptidomimetics as they read on the broad genus of structurally and functionally diverse integrin and their ligand targets.

To date, appellant has not provided sufficient evidence to support the possession of a sufficient number of species, particularly as it reads on the breadth of compounds encompassed in the claimed methods to reduce or treat stenosis or restenosis, as currently recited.

Rather, appellant has continued to maintain that there is sufficient written description for the full scope of the compounds, including undescribed molecules, peptides, peptidomimetics and molecules employed in the claimed methods.

In addition, appellant's assertion of using known compounds is inconsistent with the numerous statements that "no drug treats restenosis", including such acknowledgement by appellant in the **specification** as filed.

"No pharmacologic agent has yet been shown to reduce restenosis in humans" (see page 2, paragraph 2 of the instant **specification)**.

"Many single target therapies have been tried as a means to reduce the occurrence or severity of restenosis, unsuccessfully". See page 6, lines 25-26 of the instant **specification**.

Also, see a more complete analysis under 35 USC 112, first paragraph, written description, in the **Examiner's Answer**, mailed 12/9/04.

In addition to the written description (and enablement) of the compounds themselves, appellant also acknowledges the differences between the attempts to go from the experimental models to the achieving clinical success in stating: "No pharmacologic agent has yet been shown to reduce restenosis in humans" (see page 2, paragraph 2 of the instant **specification**).

Therefore, the disclosure of sufficient relevant identifying characteristics coupled with a known or disclosed correlation between function and structure of the broadly diverse classes of compounds is faced with an even higher burden in identifying those compounds that can reduce restenosis, when no pharmacologic agent (other than the the prior art 7E3 antibody) has been shown to reduce restenosis in humans.

The application does no more than describe the desired function of the claimed compounds broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

The claimed methods depend upon finding "a compound that specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis in patients undergoing cardiovascular surgery and procedures". Without such a compound, the skilled artisan cannot practice the claimed method of treatment. It means little to invent a method if one does not have possession of the compound(s) that is (are) essential to practice the method. Without possession of the compound(s), the claimed endpoints are illusory and there is no meaningful possession of the method.

Given the absence of providing disclosure of sufficient relevant identifying characteristics coupled with a known or disclosed correlation between function and structure of the broadly diverse classes of compounds and the absence of a sufficient number of species that represent the broad classes of molecules, peptides and peptidomimetics of structurally and functionally distinct intergrins and their ligands,

appellant has not provided sufficient written description of a "compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis in patients undergoing certain cardiovascular procedures or transplantation", broadly encompassed by the claimed invention.

In contrast to appellant's assertions on page 9, paragraph 2 of the **Reply Brief, independent claim 1** is not limited to a single integrin, Mac-1 (CD11b/CD18), other than under prior art as the elected invention.

In contrast to appellant's assertions, appellant's specification does not provide two distinct compounds, an antibody and a protein fragment.

The specification as filed discloses a fibrinogen fragment (see page 13, paragraph 3 of the instant **specification**) for which appellant has appeared to make no effort to provide supporting evidence that the only peptide disclosed in the specification as filed provides for the claimed methods of inhibiting stenosis and restenosis.

In addition to antibodies to Mac-1 (see pages 22-23 of the instant **specification**),

appellant has relied upon the post-filing date description of a urokinase receptor uPAR) derived peptide inhibitor of Mac-1 (see **Rogers et al., Circulation, 100 (Supp 1) (No. 18), 11/2/99**, #1742; Exhibit) (see page 14, paragraph 3 of the **Substitute Appeal Brief**).

As addressed on pages 39-40 of the **Examiner's Answer**, it was noted that the post-filing date **Rogers Circulation (1999) Abstract** describes:

that the site(s)of interaction between the urokinase receptor uPAR and Mac-1 is unknown and that they have identified a critical non-I domain binding site for uPAR on CD11b;

that the peptide M25 inhibited leukocyte adhesion to fibrinogen, vitronectin and cytokine-sitmulated endothelial cells, even though it did not block ligand binding to Mac-1; and

that the M25 peptide is the first extracellular domain sequence of an integrin which broadly imparts integrin adhesion and migration to matrix proteins without directly inhibiting overall ligand binding, suggesting a novel strategy for regulation of integrin function in vascular injury and inflammation associated with artherosclerosis and restenosis.

Appellant has not provided a sufficient nexus or link between the post-filing identification of the M25 peptide to the instant **specification**.

The instant **specification** does not disclose the M25 peptide, nor disclose the critical non-I domain binding site for uPAR on CD11b cited in the **1999 Abstract**.

Note again that the M25 peptide not block ligand binding to Mac-1.

Further, while this **1999 Abstract** suggest the ability of this peptide in vascular injury associated with restenosis, the M25 peptide had not been tested in a manner that was reasonably predicted to inhibit or reduce stenosis or restenosis in patients in need undergoing the cardiovascular surgeries and procedures recited in the claimed methods.

Therefore, it is unclear from the record whether this M25 peptide satisfies the claimed methods.

Clearly, the skllled artisan was not in possession of the M25 peptide at the time the invention was made, nor was the skilled artisan in possession of the identification of the distinguishing critical non-I domain binding site in a manner consistent with the standards of Written Description from the disclosure of the specification as filed at the time the invention was made.

The M25 peptides does not appear to be one of the known compounds at the time the invention was made, as apparently asserted and relied upon by appellant's new use of an old compound.

Again, it is curious that appellant has relied upon the M25 peptide described in the post-filing date **Rogers Circulation (1999) Abstract**, while appellant has made no attempt to support the ability of the one disclosed fibrinogen peptide (see page 12, paragraph 3 of the specification) to achieve the in vivo characteristics required by the claimed methods.

There is insufficient or no evidence that there is a recognized structure/function relationship between the disclosed anti-Mac-1 antibody antagonists and any others that might be found using the claimed screening methods. Structural identifying characteristics of the genus members are not disclosed, nor is there a description of other identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize that appellant was in position of the scope of the claimed invention of "compounds" employed in the claimed methods.

Here, appellant is claiming a genus where practice of the invention requires use of a compound from a genus whose existence has not yet been described to show that appellant was in possession of the claimed genus.

In noting University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (Fed. Cir. 2004), appellant is reminded that the Court does not distinguish between product claims and method claims with respect to written description.

"Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds or infringing methods from non-infringing methods" (Univ. of Rochester, 69 USPQ2d at 1894).

While appellant asserts that the claims are not drawn solely to the use of a class of **un**known compounds defined by function alone, but to classes that are known, both by structure and by function, appellant has not provided sufficient identifying or distinguishing characteristics of the claimed molecules, peptides and peptidomimetics, nor has provided a sufficient number of species for each class of compounds, but rather has provided upon generic disclosure of classes of compounds.

As pointed out by the district court, however, the '850 patent does not disclose just "which 'peptides , polynucleotides, and small organic molecules' have the desired characteristic of selectively inhibit PGHS-2. Without such disclosure, the claimed cannot be said to have been described. (Univ. of Rochester, 69 USPQ2d at 1895).

Consistent with the decision in Rochester, appellant has not provided sufficient evidence that the skilled artisan would be able to identify the claimed compounds by its vague functional description as a "compound which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis in patients undergoing certain cardiovascular procedures or transplantaton" from generic classes of molecules, peptides and peptidomimetics, broadly encompassed by the claimed invention rather than providing the identifying and distinguishing characteristics required to satisfy the statute, consistent with the decisions by the Federal Circuit and the practice and procedures set forth in the MPEP.

Rather than providing identifying or distinguishing structure-function correlations or providing possession of a representative number of species representing the broad classes of compounds, appellant has relied upon the claiming the target of the claimed compounds and broad classes of such compounds coupled with a disclosure for various generic screening means for screening for said compounds (e.g. molecules, peptides and peptidomimetics).

Again, see a more complete analysis under 35 USC § 112, first paragraph, written description, and response to appellant's arguments of record in the **Examiner's Answer**, mailed 12/9/04.

(ii). Enablement

Claims 1-6, 8 and 11-12 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As pointed out previously and reiterated above in **(3) STATUS OF CLAIMS,**
claims 1-6, 8 and 11-12 stand rejected under 35 U.S.C. § 112, first paragraph, and not claims 1-12 as indicated by appellant on page 10 of the **Reply Brief**.

However, the examiners agrees with appellant to the extent that the rejections under 35 U.S.C. § 112, first paragraph, enablement (and written description set forth in (i) above) would be applicable to non-elected / withdrawn claims 7 and 9, as these are withdrawn claims recite targets of the claimed compounds, wherein appellant has not satisfy the statute with respect to the claimed "compounds which specifically inhibits or reduces leukocytes integrin-mediated adhesion or function" themselves and broadly encompassed by the claimed methods.

For the record, it is noted that appellant has addressed various references of record applied in the rejection under 35 USC 112, first paragraph in the **Reply Brief**.

This current attention to the references in the rejection under 35 U.S.C. § 112, first paragraph, stands in contrast to the **Substitute Appeal Brief**, filed 8/10/04, wherein appellant asserted that the examiner merely expressed the opinion that the claimed method was unpredictable in the absence of evidence and that the examiner has provided only allegations, not support for his rejections on (see iii on pages 15-16 of the **Substitute Appeal Brief**).

A more thorough review of the teachings of the references, including those referenced on page 10 of the **Reply Brief** and the response to appellant's position of record can be found on pages 13-20 and 38-48 in the **Examiner's Answer**, mailed 12/9/04.

Again the examiner finds it curious that appellant continues to rely upon **Topol et al., JAMA 278: 479-484 (1997)** (Exhibit) as evidence for the position that there is sufficient enablement (and written description) for the full scope of compounds that can be used in the claimed methods.

Topol et al. states: "A large number of pharmacological agents have failed to reduce restenosis or improve long-term clinical outcomes and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abciximab, a monoclonal antibody against the β3 integrin" (see page 479, far right column, paragraph 1).

Therefore, **Topol et al.** stands for both
the rejection under 35 U.S.C. § 112, first paragraph, enablement,
in teaching that "a large number of pharmacological agents have failed to reduce restenosis" as well as
the rejection under prior art
in teaching that the abciximab antibody is the prior art 7E3 / ReoPro antibody that binds GPIIb/IIIa and cross-reacts with Mac-1 and αvβ3 and is the only pharmacological agent that has reduced restenosis in humans.

Again, appellant remains inconsistent in relying upon **Topol et al**. to stand for enabling the broad scope of compounds to treat stenosis and restenosis,
yet the one agent that has been shown to inhibit restenosis in humans cited by Topol et al. (abciximab, 7E3 antibody), which is employed in the prior art rejections herein has been considered non-enabled by appellant.
See appellant's responses to the prior art rejections to **Simon et al. (1995), Genetta et al. and Coller et al.**

As indicated above and of record, appellant's assertion of broad enablement for the claimed compounds encompassing broad classes of compounds (e.g., molecules, peptides and peptiodmimetics) as it reads on a structurally and functionally diverse genus of integrins and their ligands is inconsistent with the numerous statements that "no drug treats restenosis", including such acknowledgement by appellant in the **specification** as filed.
"No pharmacologic agent has yet been shown to reduce restenosis in humans" (see page 2, paragraph 2 of the instant **specification**).

"Many single target therapies have been tried as a means to reduce the occurrence or severity of restenosis, unsuccessfully". See page 6, lines 25-26 of the instant **specification**.

Again, see a more complete analysis under 35 USC § 112, first paragraph, enablement, in the **Examiner's Answer**, mailed 12/9/04.

Rather than the examiner focusing on mere possibilities and ignoring data,

it appears that appellant continues to ignore the clear teachings and certain conclusions that the skilled artisan would draw from only one successful pharmacologic compound which inhibits restenosis in humans in that this is an unpredictable art and this one successful prior art 7E3 antibody which binds Mac-1 meets the claimed methods as a species (including the elected species) reads on the genus.

Again, appellant relies upon **Simon et al., J. Clin. Invest. 105: 293-3000 (2000),** which describes the role of inflammation in mechanical arterial injury, including Mac-1.

However as pointed out previously on pages 44-45 of the **Examiner's Answer**,

Simon et al. (2000) also states: "Although our data showing that antibody blockade of Mac-1 or absence of Mac-1 each reduce neointimal thickening after experimental angioplasty or endovascular stent implantation, the relevance of these observations to clinical angioplasty is unknown." See page 299, column 1, paragraph 2).

Simon et al. (2000) also notes that the precise molecular mechanisms responsible for leukocyte recruitment to mechanically injured arteries that are devoid of endothelium and the result effects of inflammation on vascular repair after PTCA are unknown (see page 293, column 1, of the Introduction).

While appellant argues that **Kuntz, Science 257: 1078-1021 (1992)** supports the statements in the appellant's application,

the specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention as it reads on broad classes of molecules, peptides and peptidomimetics to inhibit or reduce stenosis and restenosis in patients undergoing cardiovascular procedures and transplantation.

One skilled in the art would not know the identity of any non-disclosed compound falling within the scope of the claim and consequently would not be able to make it. An assay for finding a product is not equivalent for making that product. If the skilled artisan cannot make the product, then the skilled artisan cannot use the product.

Further, the possible enablement of only one or a few embodiments (e.g. antibodies that bind and inhibit Mac-1-mediated interactions) does not demonstrate with reasonable specificity how to make and use other potential embodiments (e.g., peptides, peptidomimetics, molecules, nucleic acid regulators) in an unpredicatable art such as inhibiting or reducing stenosis or restenosis in patients in need undergoing cardiovascular surgeries and procedures.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies for inhibiting restenosis and stenosis, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive for the breadth of compounds (e.g., peptides, peptidomimetics, molecules, nucleic acid regulators) which specifically inhibits or reduces leukocyte-integrin-mediated adhesion that reduce or inhibit stenosis and restenosis in patients undergoing certain cardiovascular procedures and transplanation.

In addition, the following is noted in response to appellant's assertions in the **Reply Brief**.

Although appellant asserts that the claimed method does not involve the hemostatic-thrombotic system in addressing **Hemker et al**. (Emerging Drugs 4: 175-195, 1999), Hemker et al. states:

"In recent years, it has been firmly established that virtually every arterial occlusive event is due to formation of a local thrombus on a damage internal surface of the vessel. Thrombin plays an all-important role in this process. A damaged wall exposes triggers for thrombosis, such as tissue factor present in the smooth muscle cells of neointima."

See Medical Need on page 176 of **Hemker et al**.

More importantly, the following excerpt from **Fattori et al. (Lancet 361: 247-249, 2003**; see page 247-248, Mechanisms of Restenosis and Preventing Restenosis) has been set forth in the interest of setting some groundwork to the issues set forth in the instant application and provides for the contribution or involvement of the hemostatic-thrombotic system associated with stenosis and restenosis, which is an extremely complex phenomenon, involving numerous complex interactions (see page 6, lines 24-25 of the instant **specification**). For example, the Mechanisms of Restenosis certainly include elements of the hemostatic-thrombotic system and Preventing Restenosis certainly involves in targeting elements of the hemostatic-thrombotic system.

See the following set forth on pages 33-34 of the **Examiner's Answer**.

Mechanisms of Restenosis:

Restenosis is the reduction of the luminal size due to loss of gain in lumen size after intravascular interventional procedures. Several cellular and molecular events occur sequentially after a vascular injury. The initial response of the elastic fibers of the vascular wall to overstretching by balloon catheter is elastic recoil, response for the loss of gain, which characterises the early phase or restenosis. The endothelial denudation and the exposure of the subintimal components cause platelet adherence and aggregation, fibrinogen binding, and thrombus formation. Thrombus formation can also act as a scaffold into which vascular smooth muscle cells can migrate, synthesise matrix and collagen, and reorganise the thrombus, providing the substrate for neointimal formation. Activated platelets release several mitogens and chemotactic factors, which stimulate smooth muscle cell migration and proliferation into the injury site. Inflammatory mediators and cellular elements contribute to trigger a complex array of events that modulate matrix production and cellular proliferation. Finally, remodeling, a gradual dynamic process mediated by adventitial myofibroblasts that leads to a change in vessel size by constrictive remodeling without an overall change in tissue volume, contributes to the loss of lumen at later time. Stenting reduces elastic recoil and negative remodeling, the mechanical components of restenosis, but also stimulates the cellular mechanisms yielding to in-stant restenosis.

Preventing Restenosis

Much research into many mechanical devices and drugs has been done to prevent restenosis, providing the rationale for an enormous number of clinical trials, but none have been proven to be effective. Many different biological mechanisms contribute to restenosis and drugs that target only one pathway for a restricted period may have limited value in a multifactorial process. Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium-channel blockers, angiotensin-converting-enzyme inhibitors, cholesterol-lowering agents, and antioxidants has proven almost universally negative. These agents were previously tested in animal models and found to be beneficial. The lack of efficacy in human studies may be in part due to insufficient concentration of drug at the injury site or lack of chronic dosing. In general, although animal models provide new insight into the mechanism of restenosis, biological and mechanical differences meant that therapeutic success of anti-restenoic therapies was not achieved in human beings.

With respect to **Pimanda et al.** (Curr. Drugs Targets Cardiovas. Haematolod Disord. 3: 101-123 (2003), appellant asserts that the statements concerning three broad areas of emerging technologies supports the statements in appellant's application.

It is not clear which statements being supported in the instant application are being referred to by appellant.

In addressing the issue of restenosis with emerging therapies in cardiology and haemotology, **Pimanda et al. (Curr. Drug Targets Cardiovas. Haematol. Disord 3 (2): 101-123, 2003)** disclose that: "from the 1980's to the present numerous drugs tested in animal models - particularly the pig - have suggested benefit, although until recently none have shown benefit in humans" (see entire document, including Strategies to Reduce Restenosis on pages 101-102, overlapping paragraph). These authors conclude that "as the extent of the biological complexity of cell growth and regulation is understood, the unbridled enthusiasm at the dawn of the molecular era now has been tempered by a sense of reality. From the current evidence, it is likely that many drugs under development that target a particular molecular defect may prove ineffective alone and will probably need to be used in combination with cytotoxics in current use to achieve disease remission"
See the first paragraph of the Conclusion on page 117.

Pimanda et al. does appear to be consistent with page 2, paragraph 2 of the instant **specification** which states:
Attempts to limit stenosis or restenosis of blood vessels following revascularization have included administration of pharmacologic agents and technical approaches. No pharmacologic agent has yet been shown to reduce restenosis in humans.

This is also consistent with and addressed above with respect to the examiner's reliance upon **Topol et al., JAMA 278: 479-484 (1997)** and the examiner's rebuttal, including the disclosure of the **instant specification**, which stands for the unpredictability of defining those identifying or distinguishing characteristics that enable compounds which can inhibit stenosis or restenosis.

Also note that **Pimanda et al.** addresses the issue of restenosis in the context of emerging therapies in Cardiology and Haemotology (e.g. see Title, Abstract and Introduction on page 101),
in contrast to appellant's assertions that restenosis does not involve the contribution or involvement of the hemostatic-thrombotic system or the use of anti-platelet or anti-thrombotic agents.

It is noted that these post-filing date emerging technologies of gene transfer or gene modification, including targeting the growth factor VEGF, the oncogene c-myb and the transcription factor E2F are being discussed (see pages 102-103 of **Pimanda et al.**; see Gene Transfer and Gene Modification).

There is insufficient nexus to the specification and the claimed methods which rely upon compounds that target integrins and their ligands, including compounds that target Mac-1.

For example, the claimed methods rely upon compounds such as molecules, peptides and peptidomimetics targeting integrins and their ligands, not growth factors, oncogenes and transcription factors.

Also, it is noted that Pimanda et al. describes only a few limited examples and does not suggest that broad classes of gene transfer and gene modification would be applicable broadly to all growth factors, oncogenes and transcription factors.

Again, it is curious that appellant continues to rely post-filing date evidence to support the claimed compounds, yet appellant maintains that the claims are simply a new use of old compounds.

Where are the compounds known at the time the invention was made that provide objective evidence to support the claimed methods, other than that of the prior art 7E3 antibody which binds Mac-1 ?

While appellant acknowledges that **Fattori et al. (Lancet 361: 247-249 (2003)** does review that lack of working compounds for preventing restenosis,

appellant simply states that appellant does not claim these compounds.

Appellant's position with respect to Fattori et al. appears inconsistent with appellant's apparent attempt to rely upon the description of post-filing date emerging technologies of gene transfer or gene modification, including targeting the growth factor VEGF, the oncogene c-myb and the transcription factor E2F are being discussed (see pages 102-103 of **Pimanda et al.**; see Gene Transfer and Gene Modification) above,

Wherein said growth factor, oncogene and transcription factor inhibitors do not have a nexus to the integrin inhibitors of stenosis and restenosis of instant specification and claimed invention.

While appellant asserts that there are many known and well characterized compound that have been described in the literature that block binding to the claimed integrins and the structure and function of these compounds are known,

the claims encompass molecules, peptides and peptidomimetics that are not well known or characterized and according to the instant specification are subject to screening procedures,

Also, it is curious for appellant to take the position that reliance upon in vitro, mouse and rabbit experimental models are predictive of the claimed methods,

while the prior art, including co-inventors own references, teaches methods of treating restenosis in humans with the 7E3 antibody, yet appellant dismisses such recognized observations in humans.

It appears that appellant's position is to require long term in-depth rigorous investigations into the effects of integrin antagonists on human restenosis, when faced with prior art,

but simply rely upon screening for integrin inhibitors (e.g. molecules, peptides and peptidomimetics) in various assays and experimental animal models with some assurance that a sufficient number of species will be identified in a field where no pharmacologic agent has been shown to treat restenosis (except for the prior art 7E3 antibody).

With respect to the issue whether claims 6 and 10 stand or fall together, the following is noted.

Again, the enablement (and the written description above) do apply to claim 6, as they read on the claimed molecules, peptides and peptidomimetics which inhibit Mac-1 expression or interaction for the reasons of record and addressed herein.

Again, claim 10, drawn to the use of anit-Mac-1 antibodies (namely, the elected inveiton) is deemed enabled (and does satisfy written description).

(b) Rejections under 35 USC § 102 and § 103.

See a more complete analyses under 35 USC § 102 and § 103 for each of the prior art rejections in the **Examiner's Answer**, mailed 12/9/04.

Applicant asserts that the crux of the prior art rejections shows that the antibody 7E3 (e.g. c7E3, abciximab, ReoPro) has been used to treat myocardial infarction and that this method inherently anticipates the claimed method.

however, appellant has not been able to distinguish the manipulative differences between the prior art methods of treating the same or nearly the same patient populations undergoing cardiovascular procedures by administering an antibody that binds Mac-1 and inhibits Mac-1-mediated adhesion and function and the claimed methods.

Appellant asserts that the 7E3 antibodies does not "specifically inhibit or reduce leukocyte integrin-mediated adhesion.

however, applicant acknowledges that this antibody cross-reacts with Mac-1, albeit its principle activity is with its intended target, GPIIb/IIIa.

Appellant further asserts that the 7E3 antibody does not inhibit or reduce integrin-mediated adhesion or function.

Further, appellant asserts that this 7E3 antibody is not useful to prevent restenosis, but rather is used to inhibit ischemic injury.

Appellant asserts that the patients are different, the dosage and schedule are different and the criteria are different.

However, the **Substitute Appeal Brief**, filed 8/10/04, acknowledged that:

Genetta discloses results of clinical trials using abciximab, a humanized chimeric Fab fragment of 7E3, a murine antibody to the integrin glycoprotein IIb/IIIa (GPIIb/IIIa) located on platelets, to reduce the incidence of abrupt closure and restenosis associated with PTCA. Abxicimab was administered by bolus injection prior to and after angioplasty. **Genetta** does not disclose binding of Mac-1 by abciximab. Genetta does not disclose inhibiting leukocyte adhesion; **Genetta** discloses inhibiting platelet aggregation. Platelets are not leukocytes. Adhesion (binding of the leukocytes to the cells lining the blood vessels) is not aggregation (clumping together of platelets).

See pages 27-28 of the **Substitute Appeal Brief**, Genetta.

Therefore, appellant's current position that that the examiner acknowledges that there is no disclosure of treating or preventing restenosis in **Genetta et al. (Ann. Pharmacotherapy 30: 251-257, 1996)** is inconsistent with the clear teaching of the prior art and appellant's previous acknowledgement in the **Substitute Appeal Brief** that Genetta does teach inhibiting restenosis in patients undergoing the cardiovascular procedures and dosing regimens encompassed by the claimed methods.

Now, it appears in the **Reply Brief** that appellant wants to change

the previous position from one in where the prior art 7E3 antibody does inhibit restenosis but does not bind Mac-1

to one where the 7E3 antibody in the prior art does not inhibit restenosis but binds Mac-1 in addition to GPIIb/IIIa.

The following is reiterated for convenience.

See the **Examiner's Answer** for a more complete analysis as it reads on each prior art rejection.

Claims 1-6, 8, 10-12 stand rejected under 35 U.S.C. 102(a)(b) as being anticipated by **Genetta et al. (Ann Pharmacol. 30: 251-257, 1996)**, as evidenced by **Schwarz et al. (Thrombosis Research 107: 121-128, 2002)**, **Bendeck et al. (J Vasc Res 38: 590-599, 2001)**, **Wu et al. (Thrombosis Research 101: 127-138, 2001)** and **The ERASER Investigators (Circulation 100: 799-806, 1999)**.

Genetta et al. teach the results of clinical trials which have indicated that abciximab can reduce the incidence of abrupt closure and restenosis associated with PTCA performed in high risk patients, plays a role in the treatment of unstable angina and acute therapy of myocardial infarctions (see entire document, including Data Synthesis on page 251, column 1 and Clinical Trials on pages 253-254). It is noted that the patients were given bolus doses of 0.25 mg/kg antibodies prior to and after angioplasty (see pages 252-255).

Genetta et al. teach the mechanism of action of abciximab, including its ability to hinder platelets and fibrinogen from participating in platelet aggregation and to prevent von Willebrand factor binding (see page 252, column 2, Mechanism of Action).

However, Genetta et al. does not disclose the Mac-1-binding properties of abcixmab.

Schwarz et al. describe the binding of abciximab to Mac-1, in particular the I-domain (also called A-domain) of the Mac-1α subunit (see entire document, including the Abstract, Results and Discussion).

Schwarz et al. provide evidence that the GPIIb/IIIa-blocking antibody fragment abciximab could inhibit the binding of fibrinogen, iC3b and the coagulation factor X to Mac-1 and that the adhesion of the THP-1 cells to immobilized ICAM-1 and to fibrinogen was reduced significantly by abcixmab (see entire document, including the Abstract).

In determining the mechanisms of action by which the beneficial treatment with c7E3 (abciximab, ReoPro) has been associated with a reduction in coronary events and the need for revascularization, both **Bendeck et al.** and **Wu et al.** teach that the 7E3 antibody can reduce smooth muscle cell migration following vascular injury which resulted in a decrease in intimal size (see entire document, including Abstract and Discussion).

The **ERASER Investigators** note that potent platelet inhibition with abciximab does not reduce in-stent restenosis in their study (see entire document, including the Abstract). However, the reference notes that these results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ (see page 805, paragraph 1).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using abciximab in a number of thrombotic conditions, resulting in the inhibition or reduction of stenosis and/or restenosis. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Thus, the clinical use and ability of abciximab to reduce the incidence of abrupt closure and restenosis associated with PTCA performed in high risk patients and to play a role in the treatment of unstable angina and acute therapy of myocardial infarctions anticipates the claimed methods in the absence of a manipulative difference between the prior art methods and the broadest reasonable interpretation of the instant methods.

Even though the 7E3 antibody was initially raised against the GPIIb/IIIa antigen and can bind GPIIb/IIIa and can inhibit GPIIB/IIIa-mediated interactions, the 7E3 antibody can similarly bind Mac-1 and inhibit Mac-1-mediated interactions as well as vitronectin-mediated interactions.

It appears that appellant's arguments to limit the claimed methods to antibodies that bind Mac-1 but do not bind Mac-1 in addition to other antigens is inconsistent with the well-known and art-recognized specificity of antibody interaction with epitopes defined by particular amino acid sequences. That an antibody "cross-reacts", i.e., binds to more than one protein sequence, does not mean that the antibody does not "specifically react" with both proteins.

First of all, the claims neither recite nor require that anti-Mac-1 antibody bind Mac-1 to the exclusivity of any other antigen.

Also, neither appellant nor the specification as filed define the metes and bounds of specifically inhibits or reduces leukocyte integrin-meidated adhesion or function.

In fact, claim 1 simply recites that the "antibody is immunoreactive with an integrin" and

claim 10 recites "an antibody immunoreactive with Mac-1 (CD11b/CD18)".

An epitope or antigenic determinant is that portion of an antigen that make contact with a particular antibody (or T cell receptor).

As well known for over 50 years in the antibody art,

athough antibody-antigen reactions are highly specific, an antibody elicted by one antigen can cross-react with an unrelated antigen. Such cross-reactions occur if two different antigens share an identical epitope or if antibodies specific for one epitope also bind to an unrelated epitope possessing similar chemical properties.

See page 138, Cross-Reactivity of, Kuby, Immunology, Second Edition, W.H. Freeman and Company, New York, 1991.

For example, Bost et al. (Immunol. Invest. 17:577-586, 1988) describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies which bound either the HIV or IL-2 derived sequence did not cross-react with irrelevant peptides (e.g., "Results, page 579).

Similarly, Bendayan (J. Histochem. Cytochem. 43:881-886, 1995) characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagon, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph).

Consequently, it was well known in the art at the time the invention was made that antibody binding of distinct proteins was indeed specific.

Relying upon cross-reactivity is consistent with the instant disclosure as filed in which appellant's exemplary M1/70 anti-Mac-1 antibody is cross-reactive between mouse and humans (pages 9-10, overlapping paragraph of the instant specification) and in which cross-reactive antibodies are desirable (see page 10, paragraph 1, of the instant specification).

The multiple binding and inhibitory properties of the 7E3 antibody is also consistent with appellant's submission of the post-filing date M25 peptide to support the written description and enablement of the claimed compounds.

As pointed out previously as addressed on pages 39-40 of the **Examiner's Answer and above**, it was noted that the post-filing date **Rogers Circulation (1999) Abstract** describes:

that the site(s)of interaction between the urokinase receptor uPAR and Mac-1 is unknown and that they have identified a critical non-I domain binding site for uPAR on CD11b;

that the peptide M25 inhibited leukocyte adhesion to fibrinogen, vitronectin and cytokine-sitmulated endothelial cells, even though it did not block ligand binding to Mac-1; and

that the M25 peptide is the first extracellular domain sequence of an integrin which broadly imparts integrin adhesion and migration to matrix proteins without directly inhibiting overall ligand binding, suggesting a novel strategy for regulation of integrin function in vascular injury and inflammation associated with artherosclerosis and restenosis.

Therefore, appellant appears to rely upon a compound having multiple properties with integrins to support the claimed methods under 35 USC 112, first paragraph,

however, appellant submits that a compound such as the 7E3 antibody having multiple properties, including binding Mac-1, inhibiting Mac-1-mediated adhesion and function and cited as the only pharmacologic agent to treat restenosis in humans does not meet the claimed methods.

Again, it is noted that appellant asserted that the 7E3 antibody did not bind Mac-1 in the **Substitute Appeal Brief**, but now appellant asserts that the 7E3 does bind Mac-1 but does not bind it specifically.

Yet, the prior art rejections provide sufficient evidence that the 7E3 antibody does bind Mac-1 and inhibit Mac-1-mediated adhesion and function.

Further, this is underscored by **co-inventor's Simon et al. prior art teaching** as follows.

Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995), teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 and vitronectin and inhibits Mac-1-dependent adhesion to fibrinogen and ICAM-1. (see Abstract).

Again, appellant somehow does not read that this reference by the co-inventor Simon teaches an antibody that binds Mac-1 can inhibit stenosis or restenosis.

The examiner can only request that appellant carefully read the Abstract once again for its clear teaching.

While the evidentiary references Schwarz et al. (Thrombosis Research 107: 121-128, 2002), Bendeck et al. (J Vasc Res 38: 590-599, 2001), Wu et al. (Thrombosis Research 101: 127-138, 2001) and The ERASER Investigators (Circulation 100: 799-806, 1999) cited in the prior art rejection to address appellant's previous arguments that the 7E3 antibody did not bind Mac-1 nor inhibited Mac-1-mediated interactions and restenosis,

now appellant appears to accept that the prior art 7E3 antibody does bind Mac-1 and this is an inherent property of the antibody.

Now, appellant attempts to distinguish these secondary references of **Wu et al.**, **Schwarz et al.** and Bendeck et al. in terms of effective amounts and administration, animal models, or antibody specificity but does not distinguish the manipulative differences between the prior art and instant methods for the reasons of record and discussed herein.

Again, appellant's arguments and the examiner's rebuttal concerning the evidentiary references concerning the ability of the 7E3 antibody to bind and inhibit Mac-1-mediated interactions and adhesion as well inhibiting or reducing stenosis or restenosis in treating patients in need undergoing cardiovascular surgeries and procedures is addressed above in the rejection under 35 USC 102(a)(b) **Genetta** et al. in the Response to Arguments in the **Examiner's Answer**

Once again, appellant's assertions are inconsistent with the facts and the broadest and plain interpretation of the claimed methods in view of the evidence of record as well as previous positions in the prosecution record of the instant application.

While appellant asserts that the patients are different, the dosage and schedule or treatment are different, the criteria are different,

appellant has still not been able to indicate a manipulative a difference in the prior art teachings and that claimed.

Now in raising new issues in the **Reply Brief**, appellant asserts that appellant requires administration over a period of time "typically until healing has occurred, which may be as long as six months following vascular intervention, although typically will be for four to six weeks or until acute inflammation has subsided (page 21, last paragraph to page 22, first paragraph of the **specification**).

Appellant asserts that the administration of the antibody, even if it met every other claim limitation (which it does not) would not be effective in preventing restenosis because it is not administered in an effective amount – which is not only dosage but length of time of administration. To prevent restenosis, one must administer over a prolonged period of time – weeks to months.

Appellant's current position that the prior art does not describe prolonged administration, which is essential for preventing or treating stenosis or restenosis.

As pointed out previously by appellant, an effective amount of the compound which inhibits or reduces stenosis / restenosis following injury to a vascular tissue is defined in the specification on pages 20-21 of the instant specification (see page 24, paragraph 2 of the **Substitute Brief**).

As appellant noted that: "The key parameter that is encompassed by the disorders recited in the claims is the involvement of leukocyte integrin-mediated adhesion, which, in turn, are targeted by inhibitor of leukocyte integrin-mediated adhesion (see page 25, paragraph 2 of the **Substitute Brief**). The claims are drawn to the use of inhibitors of leukocyte integrin-mediated adhesion, a readily measurable function."

As page 25, paragraph 3 of the **Substitute Brief** continues: "The common feature between the disorders listed in claim 3 is the role of integrin-mediated leukocyte adhesion. Administering a compound to specifically inhibit / reduce integrin binding will be effect to treat, at least to some degree, all of these disorders The effective amount can be routinely titrated for each patient depending on the compound and route of administration regardless of the disorder, to achieve therapeutic efficacy."

Now appellant asserts that the prior art references such as Genetta et al. are drawn to treating acute conditions while the instant methods requies administration over a period of time "typically until healing has occurred, which may be as long as six months following vascular intervention, although more typically will be for four to six weeks or until acute inflammation has subsided" (pages 21-22, overlapping paragraph of the instant specification).

In addition, appellant asserts that the administration of the antibody, even if it met every other claim limitation would not be effective in preventing restenosis because it is not administered in an effective amount – which is not only dosage but length of time of administration. To prevent restenosis, one must administer the treatment over a prolonged period of time, weeks to months.

Appellant is reminded

that the prior art does teach the use of antibodies that bind Mac-1 can reduce or inhibit restenosis in human patients,

that the claims recite "inhibiting or reducing stenosis or restenosis", which is broader than preventing restenosis;

that the patient populations are the same patients undergoing the same cardiovascular procedures and interventions;

that these patient populations are receiving the same or nearly the same dosages via the same modes of administration (e.g. prior to and after vascular intervention) as claimed.

Appellant appears to relying upon limitations (e.g. preventing, weeks to months) not claimed in order to distinguish the prior art from the instant methods.

Also as pointed out on page 38 of the **Examiner's Answer** for prior art purposes, given the current claim language, all that is required for the claims under art is to administer an inhibitor of leukocyte integrin-mediated adhesion, particularly an antibody that binds and inhibits Mac-1-mediated interactions as the elected invention, in effective amounts (e.g. 0.25 mg/kg - 1.0 mg/kg) (e.g. see page 21, paragraph 2 of the instant **specification**) in the patient populations recited in claims 1, 3 or 6 (e.g. undergoing bypass, angioplasty, atherectomy or stenting).

Here it was noted that that the appellant and the examiner appeared to be on the same page in that a compound such as an antibody (e.g. antibody that binds Mac-1 and inhibits Mac-1-mediated adhesion) which inhibits or reduces integrin-mediated leukocyte adhesion and is administered to a patient undergoing one of the claimed cardiovascular surgeries or procedures (e.g. bypass surgery, angioplasty, atherectomy or endovascular stenting) anticipates or renders obvious the claimed methods.

Appellant does not distinguish the effective amounts between the prior art methods and the instant methods other than to indicate the instant methods are drawn to effective amounts to prevent restenosis (which is not claimed), while the prior art does not provide such effective amounts.

Appellant makes no attempt to distinguish the effective amounts disclosed in the specification, the endpoints of inhibiting integrin-mediated interactions or functions (which is claimed), inhibiting or reducing stenosis or restenosis (which is claimed) or until acute inflammation has subsided (which is disclosed and cited by appellant above) from the very same effective amounts and endpoints anticipated or rendered obvious by the prior art.

Further, appellant clearly relies upon providing the appropriate effective amounts over a broad dosage range to meet the needs of the patient by the ordinary artisan at the time the invention was made.

Again, as pointed out previously in the **Examiner's Answer**, the prior art teachings do provide for the same or nearly the same dosages of integrin antagonists, including administration both prior to and after the claimed cardiovascular procedures and transplantation in order to meet the needs of the patient as determined by the ordinary artisan.

Appellant continues to ignore the plain and clear prior art teachings of administering either the 7E3 antibody or anti-Mac-1 antibodies in the treatment of the same patient populations undergoing cardiovascular procedures or transplantation to achieve both acute and long term therapeutic amelioration of the complications of their conditions.

With respect to appellant's arguments concerning the term "stenosis" in Coller et al. (U.S. Patent No. 5,976,532), appellant is reminded of the following definitions set forth in

Section 11. (A) The Invention and Clarification of Terms on page 31 of the **Examiner's Answer**.

Stenosis and Restenosis

1) As indicated previously, the Board of Appeals has made the following of record (see Vacatur and Remand to the Examiner, mailed 9/3/03).

Taber's Cyclopedic Medical Dictionary, 18th Ed., pages 130, 1666 and 1828 (1997) set forth the following definitions.

Stenosis: The constriction or narrowing of a passage or orifice.
Aortic Stenosis: Narrowing of the aorta or its orifice due to lesion of the wall with scar formation.
Restenosis: The recurrence of a stenotic condition as in a hear valve or vessel.

Given the broadest reasonable interpretation of the claims, including the context of the patient populations referenced by Coller et al., which are the same or nearly the same as the claimed methods, inhibiting stenosis as well as restenosis is met by the prior art teachings.

With respect to appellant's comments concerning Anderson, Kling et al.., Alteri, and Faxon of record, one cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145. Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination.

See the prior art rejections in the **Examiner's Answer** for a more complete analysis of the applicability of these references to the prior art rejection.

It is noted that the amended and currently pending claims more clearly recite the true nature of the claimed methods in that administering antibodies that bind and inhibit Mac-1 to cardiovascular patients in need would have the inherent or expected property of inhibiting or reducing stenosis or restenosis arising from the claimed surgeries or procedures.

On the record set forth in the instant prosecution and addressed in the **Examiner's Answer**, it is reasonable to conclude that the same patient is being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art references. Here, the stimulus or insult that leads to cellular and molecular events that occur sequentially after a vascular injury that is being targeted is the same or nearly the same cardiovascular surgeries or procedures between the prior art and the instant methods. The fact that appellant may have recited yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method. The claim language is only a statement of purpose and intended result. The expression does not result in a manipulative difference in the steps of the claims

In response to appellant's arguments in the **Reply Brief** concerning the rejection under 35 U.S.C. 103, the following is reiterated from pages 62-65 of the **Examiner's Answer**.

Appellant asserts that there is simply no teaching by the references to lead those in the art to what is claimed.

Appellant asserts that the prior art primary references of **Co et al.** , **Todd et al. Simon et al.** as well as the secondary reference **Mazzone et al.** do not describe a single agent or an antibody that inhibits stenosis or restenosis after injury.

Appellant acknowledges that **Ikeda et al.** show Mac-1 as a non-specific marker of leukocyte activation is increased after PTCA. However, appellant asserts that no data has been shown that Mac-1 is involved in restenosis.

Appellant asserts that both **Inoue et al.** and **Rogers et al.** do not disclose an antibody specific to Mac-1.

Appellant asserts that efforts at limiting the undesirable proliferative and disease states of vascular endothelium have focused on the isolated administration of analogs of endothelial compounds to support the position that one skilled in the art would not expect only a single compound to be effective in limiting or preventing restenosis.

As indicated above, **Co et al.** teach methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (see entire document, including columns 17-18, overlapping paragraph and column 18, paragraph 3-4) wherein the L-selectin-specific antibodies can used in combination with other humanized or human antibodies reactive with CD11b (i.e. Mac-1) (column 18, paragraph 1).

As indicated above, **Todd et al**. teach methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocyte-mediated inflammatory conditions, including inflammation from myocardial infarction or ischemia-reperfusion injury and the insertion of balloon catheters in the circulatory system with CD11b- / Mac-1- specific antibodies (see entire document, including Claims).

Although these references do not disclose the limitations of stenosis and restenosis per se, these claimed endpoints would be expected, intrinsic or desired endpoints by administering effective amounts of CD11b / Mac-1-specific antibodies in the same patient populations targeted and encompassed by the claimed methods. Given the referenced methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty; the ordinary artisan would have had an expectation of success that anti-CD11b antibodies would have inhibited or reduced restenosis or stenosis arising from patients undergoing said cardiovascular surgeries and procedures.

In teaching that 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1;

that the Mac-1-dependent adhesion to fibrinogen and ICAM-1, ligands which are abundant in vessels walls and that Mac-1-expressing cells accumulate in restenosis lesions and have the potential to interact with other vascular cells by secreting growth factors and cytokines; and

that the cross-reactivity of c7E3 with Mac-1 may play an additional role in inducing passivity of the vessel wall;

Simon et al. provided additional motivation and expectation of success in targeting Mac-1 in therapeutic interventions associated with the complications of angioplasty including restenosis at the time the invention was made.

The following references cited above provided further support for targeting Mac-1 in the treatment of complications of angioplasty including restenosis.

Mazzone et al. teach the CD11b/CD18 plays a major role in the leukocyte adhesion process and can be upregulated severalfold in response to chemotactic factors (see Background). Mazzone et al. further teach that patients with unstable angina have an increased expression of granulocyte and monocyte CD11b/CD18, indicating that an inflammatory reaction takes place with their coronary tree. Activation of these leukocytes may induce coronary vasoconstriction, favor thrombotic processes, and further activate platelets, thus having potential implications on the pathogenesis of unstable coronary artery disease (see Conclusion). The Discussion provides a teaching of the importance of CD11/CD18 in tissue injury in vivo in a number of animal models, including that the addition of anti-CD18 antibodies can reduce tissue injury and mortality in ischemia reperfusion injury-induced shock and myocardial infarct size (see Discussion on page 360, column 1).

Ikeda et al. teach the surface expression of CD11b of neutrophils increased significantly after percutaneous transluminal coronary angioplasty (PTCA) (see entire document, including Abstract, Results and Discussion). Ikeda et al. teach anti-CD11b antibody inhibits several neutrophil functions, including the binding of C3bi-opsonized particles, adhesive interactions of neutrophils, spreading on vascular endothelium and chemotaxis (see Discussion, particularly page 1095, column 2). Ikeda et al. further teach that anti-CD11b antibodies significantly reduced neutrophil accumulation within the infarct area (see Discussion, particularly page 1095, column 2). With respect to restenosis, Ikeda et al. teach that neutrophil activation after PTCA in humans appears to play an important role in the initial step of inflammatory phase and then to trigger the pathophysiologic chain reaction eventually resulting in coronary restenosis (see Clinical Implications on page 1096-1097). Ikeda et al. note here that activated neutrophils can potentiate platelet activity, in turn, leading to vasoconstriction and proliferation of vascular smooth muscle.

Inoue et al. teach inflammatory stimuli within the coronary vessels associated with coronary angioplasty upregulate Mac-1 expression on the surface of PMNs and this process is more marked in patients who experience later restenosis (see entire document, including Conclusions). The activation of neutrophil adhesion molecule after PTCA has valued as a predictor of subsequent restenosis (see Conclusion). Inoue et al. teach that the same cytokines that stimulate the expression of leukocyte adhesion molecules, such as Mac-1 also stimulate smooth muscle cell proliferation.

Rogers et al. teach that the inhibition of neointimal hyperplasia and thrombosis depends on the type of vascular injury and the site of drug administration (see entire document, including Abstract and Discussion). Here, Rogers et al. teach different forms of injury may require different therapeutics and complication of arterial intervention such as excessive neointimal hyperplasia and thrombosis may demand alternative therapeutic regimens. Duration, dose, and site of delivery rather that frank resistance to therapy may explain why experimental effective antiproliferative and antithrombotic agents fail clinically.

Appellant submits that this demonstrated by **Co et al**. where antibodies are administered in combination with thrombolytic agents or angioplasty.

Appellant is reminded that the claims recite "comprising and do not exclude unrecited ingredients or method steps. Further, such thrombolytic agents or procedures such as angioplasty were employed in therapeutic regimens associated with the patients targeted by the prior art and the claimed invention.

Although certain references do not disclose the targeted endpoint of reducing or inhibiting stenosis or restenosis per se, it was clear that the references do teach targeting Mac-1 with effective amounts encompassed by the claimed invention (e.g. 0.25 mg/kg or more in single or multiple doses) in order to inhibit various inflammatory consequences of Mac-1 expressing cells in therapeutic regimens associated with stenosis or restenosis such as angioplasty or bypass surgery. In addition, the combined references do teach targeting either stenosis, restenosis or endpoints associated with stenosis or restenosis (occlusion, intimal hyperplasia). The claimed methods comprises the same steps, the same effective amounts and the same targeted patient populations as the prior art. In addition, **Rogers et al.** teach duration, dose, and site of delivery are important in achieving therapeutic endpoints aimed at limiting restenosis such as inhibiting intimal hyperplasia (see entire document). Given the well known complications of stenosis and restenosis associated with various procedures such as angioplasty or bypass surgery at the time the invention was made, one of ordinary skill in the art would have had an expectation of success that treating these conditions or procedures with effective amounts of anti-Mac-1 antibodies would have resulted in the inhibition or reduction of certain endpoints associated with stenosis or restenosis arising in patients undergoing certain cardiovascular surgeries and procedures.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Appellant's arguments have not been found persuasive.

For the above reasons, it is believed that the rejection should be sustained.

Respectively submitted,

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